CNS*2001 Poster Submission

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Program Book Abstract

Resurrecting Marr's bones: a new look at "A Theory of Cerebellar Cortex"

We present a model of cerebellar learning that recasts David Marr's 1969 theory in light of recent physiological and anatomical evidence. Marr predicted that coincidence of parallel fiber (PF) and climbing fiber (CF) inputs to a Purkinje cell (PC) leads to LTP of PF-PC synapses; instead, subsequent experiments found LTD. However, the role Marr envisioned for the CF may be provided by granule cell axon ascending branches (AB), which make multiple synapses on the overlying PC. We predict that AB-PF correlations lead to LTP, and show computer simulations combining AB-PF LTP for feedforward state prediction with CF LTD for feedback error correction.

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Full Summary for Submission Review

Resurrecting Marr's bones: a new look at "A Theory of Cerebellar Cortex"

In 1969 David Marr published his revolutionary theory of cerebellar cortex [1], combining the known cerebellar physiology and anatomy with machine learning methods of his day. Soon after, experiments designed to test his hypotheses seemingly contradicted some of his major predictions – predictions without which he had concluded "the theory collapses", although "something of the bones of the theory would remain." Three decades later, the vestiges of Marr's theory continue to exert influence, having been modified and extended into many new models of cerebellar function. However, the wide diversity of such models and the morass of current competing theories [2] indicate that important pieces of the cerebellum puzzle are still missing. We propose that more recent studies of cerebellar physiology, anatomy, and learning, mandate a fresh recasting of Marr's original ideas, in effect "resurrecting the bones" of his theory.

We will first review Marr's theory with emphasis on the hypothesized sites of synaptic modification and mechanisms for learning. Marr's foremost prediction was that parallel fiber (PF) synapses onto Purkinje cells (PC) would be facilitated, in a Hebbian manner, when presynaptic PF activity is coincident with postsynaptic PC depolarization induced by climbing fiber (CF) input. Subsequent experiments, however, seemed to contradict this prediction. The most damning result was growing evidence for long term depression (LTD) of synaptic efficacy during simultaneous stimulation of parallel fiber and CF inputs [3]. Alternative Marr-like models instead used LTD to provide the learning capability [4], and by 1989, LTD was widely regarded as the "memory element for cerebellar motor learning" [3]. However, the functional role of CF input remains controversial, as other evidence supports the idea that CF activity represents error signals for feedback control or to change states of activity. These roles are not consistent with the one Marr had envisioned for the CF.

Using Marr's theory as the foundation, we will next present a model of cerebellar function that incorporates elements from neural network theory [5], control theory [6], and experimental results in cerebellar-like structures [7]. We follow along the line of Keeler, who in 1990 extended a Marr-Albus-Kanerva (MAK) type model to perform dynamic state prediction [8]. Our model can be described as an adaptive state predictor: information from the entire body, including sensory, proprioceptive and cortical inputs (such as motor commands) provides the context from which to predict the next state. Cerebellar output then can be used for several purposes: to filter future input, improving detection of novel or unexpected events, to modulate or learn motor outputs, or to provide feedback for learning. But how can our model be reconciled with the experimental results that cursed Marr's original theory?

The most critical missing puzzle piece may be new evidence for a third major PC input.

The axons of granule cells have long been known to exhibit synaptic densities as they ascend to the molecular layer [9], but the significance of these synapses was largely ignored. Llinas [10] first suggested that the ascending axon branches (AB) may make numerous contacts with overlying PC dendrites. After mapping "patchy" receptive field responses in perioral regions of rat cerebellum, Bower and Woolston [11] postulated that the ABs of neighboring granule cells provide a relatively large, excitatory, synchronous input to their overlying PC, usually resulting in sufficient depolarization to produce sodium spikes in the PC. We propose that it is this AB-induced postsynaptic activity, perhaps even through local depolarization of individual dendritic branches, that causes facilitation when coupled with PF input.

For anatomical corroboration, Marr had prophetically suggested that a "rather dangerous place one might look for implications of the [synaptic] modification hypothesis is in ... electron-micrographs of cells..." We were inspired to reexamine Marr's theory due to recent EM results from Gundappa-Sulur and Bower [12, 13]. The AB synapses were found to be located only on the smallest terminal dendritic processes of the Purkinje cell. In contrast, PF-PC synapses were restricted to larger dendrites, and also contained fewer presynaptic vesicles with a higher variability in number. PF inputs adjacent to AB inputs are therefore well situated to modulate or gate the AB response, and the variability in PF-PC synapses suggests they are graded and modifiable. Thus we believe these circumstances provide an ideal environment for Hebbian facilitation or long term potentiation (LTP). In this manner the cerebellar circuitry can function as the associative memory Marr postulated, by learning patterns of sensory and motor inputs presented by the mossy fiber pathway. Notably, this is very complementary to the LTD result and the theories of climbing fiber input representing error signals, since the climbing fiber pathway is now free to assume other roles. By assigning the ascending branch and parallel fibers to feedforward state prediction, and climbing fiber input to feedback error correction or change of states, our model can both account for more of the experimental evidence and has increased learning capacity compared to models which ignore the AB input pathway.

Physiological evidence for PF-PC LTP has been reported in studies of synaptic plasticity in cerebellar slice preparations. Crepel and Jaillard [14] found that LTD was induced when PF tract stimulation was paired with calcium spikes caused by strong depolarization of PCs, but LTP was more prevalent when the pairing was with sodium spikes caused by moderate depolarization. (Note that complex calcium spikes are produced in the dendrite in response to climbing fiber inputs and are physiologically distinct from simple sodium spikes.) The authors concluded that "PCs can reinforce this LTP or alternatively can convert it into LTD depending on their firing on sodium or [calcium] spikes" (p. 124 in [14]). Our model can account for these experimental results: direct stimulation of the PF tract is likely to antidromically backfire the AB inputs, causing local correlated activity and simple spikes, and thus leading to Hebbian LTP. Climbing fiber activity, on the other hand, greatly depolarizes the Purkinje cell, and thereby enables LTD in the manner reported previously. We will outline an experimental protocol to test these predictions using techniques to isolate the three PC inputs *in vivo*.

To demonstrate the utility of our cerebellar model, we will also present a computer simulation that combines the two distinct learning methods. The model was trained to perform dynamic state estimation on a virtual dynamic arm, with the goal to learn to throw a ball at a target. Given a particular arm trajectory, the critical variable for an accurate throw is the timing of release [15]. Over multiple trials the model learns to track and predict the arm trajectory, to modulate the trajectory for different target heights, and to release the ball at an appropriate point within the trajectory.

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